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NEWS	5	AUG 20	CA/Caplus enhanced with CAS indexing in pre-1907 records
NEWS	6	AUG 27	Full-text patent databases enhanced with predefined patent family display formats from INPADOCDB
NEWS	7	AUG 27	USPATOLD now available on STN
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NEWS	22	DEC 17	USPATOLD added to additional database clusters
NEWS	23	DEC 17	IMSDRUGCONF removed from database clusters and STN
NEWS	24	DEC 17	DGENE now includes more than 10 million sequences
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NEWS	27	DEC 17	CA/Caplus enhanced with new custom IPC display formats
NEWS	28	DEC 17	STN Viewer enhanced with full-text patent content from USPATOLD
NEWS	29	JAN 02	STN pricing information for 2008 now available
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NEWS	31	JAN 28	USPATFULL, USPAT2, and USPATOLD enhanced with new custom IPC display formats
NEWS	32	JAN 28	MARPAT searching enhanced
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NEWS 35 JAN 28 MEDLINE and LMEDLINE reloaded with enhancements  
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FULL ESTIMATED COST	0.21	0.21

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181 or 227 or 234 or 237 or 114 adj 170)  
L1 86 (INSULIN(w)GROWTH(w)FACTOR(w)BINDING(w)PROTEIN(w)2 OR IGFBP  
(w)2) AND (180 OR 181 OR 227 OR 234 OR 237 OR 114 ADJ 170)

=> dup rem l1  
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L2 31 DUP REM L1 (55 DUPLICATES REMOVED)

=> s l2 and py<2003  
1 FILES SEARCHED...  
L3 21 L2 AND PY<2003

=> dis his

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FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 14:42:11 ON 16 FEB 2008

L1 86 S (INSULIN(W)GROWTH(W)FACTOR(W)BINDING(W)PROTEIN(W)2 OR IGFBP(W)  
L2 31 DUP REM L1 (55 DUPLICATES REMOVED)  
L3 21 S L2 AND PY<2003

=> dis ibib abs l3 1-21

L3 ANSWER 1 OF 21 MEDLINE on STN  
ACCESSION NUMBER: 2002382543 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 12127047  
TITLE: The IGF-system in healthy pre- and postmenopausal women: relations to demographic variables and sex-steroids.  
AUTHOR: Helle Svein I; Ekse Dagfinn; Holly Jeff M P; Lonning Per E  
CORPORATE SOURCE: Department of Oncology, Haukeland University Hospital, N-5021 Bergen, Norway.  
SOURCE: The Journal of steroid biochemistry and molecular biology, (2002 May) Vol. 81, No. 1, pp. 95-102. Journal code: 9015483. ISSN: 0960-0760.  
PUB. COUNTRY: England; United Kingdom  
DOCUMENT TYPE: (COMPARATIVE STUDY)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200209  
ENTRY DATE: Entered STN: 20 Jul 2002  
Last Updated on STN: 26 Sep 2002  
Entered Medline: 25 Sep 2002  
AB Plasma insulin-like growth factor (IGF)-I, free IGF-I and -II, IGF-binding protein (IGFBP)-1, -2, and -3 together with IGFBP-3 protease activity were measured in 114 postmenopausal and 39 premenopausal healthy women. For each parameter, the mathematical distribution was characterised, and the normal range for pre- and postmenopausal women described, together with correlations to demographic variables and sex-steroids (postmenopausal women). Postmenopausal women had lower levels of plasma IGF-I ( $P<0.001$ ) and free IGF-I ( $P<0.001$ ) compared to premenopausal women, while plasma IGFBP-2 ( $P<0.05$ ) and immunoreactive IGFBP-3 ( $P<0.001$ ) were higher in postmenopausal women. Free IGF-I (but none of the other parameters) was significantly lower in postmenopausal smokers compared to non-smokers ( $P<0.05$ ). IGF-I and -II both correlated positively to height ( $r=0.203$ ,  $P<0.05$  and  $r=0.198$ ,  $P<0.05$ , respectively), while IGF-II correlated positively to weight ( $r=0.250$ ,  $P<0.01$ ). Plasma IGF-I correlated positively to androstenedione ( $r=0.292$ ,  $P<0.01$ ) and dehydroepiandrosterone sulphate (DHEAS,  $r=0.202$ ,  $P<0.05$ ), while a significant positive correlation was observed between IGF-II on the one side and oestradiol ( $E(2)$ ,  $r=0.227$ ), oestrone sulphate ( $E(1)S$ ,  $r=0.238$ ) and androstenedione ( $r=0.213$ ) on the other side ( $P<0.05$  for all). Our results support a relation between sex-steroids and IGF-I and -II in healthy postmenopausal women. The lower levels of total and free IGF-I in postmenopausal compared to premenopausal women indicate lower bioavailability of this growth factor in elderly females.

L3 ANSWER 2 OF 21 MEDLINE on STN  
ACCESSION NUMBER: 2002308787 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 12030778  
TITLE: Short-term infusion of LongR(3) insulin-like growth factor (IGF)-I decreases hepatic IGF-I mRNA but not IGF binding protein-3 mRNA expression in pigs.

AUTHOR: Dunaiski V; Dunshea F R; Walton P E; Goddard C  
 CORPORATE SOURCE: Cooperative Research Centre for Tissue Growth and Repair,  
 Child Health Research Institute, 72 King William Road,  
 North Adelaide, South Australia 5006, Australia.  
 SOURCE: General and comparative endocrinology, (2002 Apr)  
 Vol. 126, No. 2, pp. 221-8.  
 Journal code: 0370735. ISSN: 0016-6480.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 (RESEARCH SUPPORT, NON-U.S. GOV'T)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200210  
 ENTRY DATE: Entered STN: 11 Jun 2002  
 Last Updated on STN: 8 Oct 2002  
 Entered Medline: 4 Oct 2002

AB Infusion of pigs with an insulin-like growth factor-I (IGF-I) analogue (LongR(3)IGF-I) that does not bind to IGF-binding proteins decreases growth rate and the plasma concentration of growth hormone (GH), IGF-I, IGFBP-3, and insulin. This study was designed to determine whether the decrease is due to changes in IGF-I and IGFBP-3 gene expression. IGF-I or LongR(3)IGF-I (180 microg/kg/day) was infused into 55-kg finisher pigs for 4 days using Travenol infuser pumps. Plasma IGF-I concentration was measured by radioimmunoassay and plasma IGFBP-3 and IGFBP-2 were estimated by Western ligand blotting. Steady-state levels of IGF-I and IGFBP-3 mRNA were measured by RNase protection assay. Neither IGF-I nor LongR(3)IGF-I had a significant effect on hepatic IGF-I class 1 mRNA expression, whereas hepatic IGF-I class 2 mRNA expression was significantly reduced by both peptides. Plasma IGFBP-3 levels were unaffected by IGF-I treatment but were reduced by LongR(3)IGF-I treatment. The decrease in IGFBP-3 was not due to decreased gene expression in porcine liver or kidney, since neither IGF-I nor LongR(3)IGF-I treatment altered IGFBP-3 mRNA. This study infers a direct effect of the IGF analogue LongR(3)IGF-I on GH through its inhibition of plasma IGF-I concentration and class 2 IGF-I mRNA. The decrease in plasma IGFBP-3 was not accompanied by a decrease in hepatic or renal IGFBP-3 mRNA, suggesting that in this case, plasma IGFBP-3 protein levels are posttranslationally regulated or are derived from tissues other than liver or kidney.  
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L3 ANSWER 3 OF 21 MEDLINE on STN  
 ACCESSION NUMBER: 2001573103 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 11678829  
 TITLE: Paradoxical elevations in serum IGF-II and IGF binding protein-2 in acromegaly: insights into the regulation of these peptides.  
 AUTHOR: Renehan A G; Toogood A A; Ryder W D; Jones J; Potten C S; O'Dwyer S T; Shalet S M  
 CORPORATE SOURCE: Department of Surgery, Christie Hospital NHS Trust, Manchester, UK.. arenehan@picr.man.ac.uk  
 SOURCE: Clinical endocrinology, (2001 Oct) Vol. 55, No. 4, pp. 469-75.  
 Journal code: 0346653. ISSN: 0300-0664.  
 PUB. COUNTRY: England; United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 (RESEARCH SUPPORT, NON-U.S. GOV'T)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200111  
 ENTRY DATE: Entered STN: 30 Oct 2001  
 Last Updated on STN: 5 Nov 2001

Entered Medline: 1 Nov 2001

AB OBJECTIVE: Circulating insulin-like growth factor (IGF)-II and IGF binding protein-2 (IGFBP-2) are frequently altered, often in parallel, in numerous pathologies including neoplastic disease but little is known about their normal regulation. This study compared serum IGF-II and IGFBP-2 distributions between acromegalics and a large normal adult population to explore possible determinants. PATIENTS: Sixty acromegalic patients undergoing screening colonoscopy (age range 25-81 years); normative data from 306 healthy adults (age range 20-89 years). MEASUREMENTS: Serum IGF-I, IGF-II, IGFBP-2 and IGFBP-3 were measured in healthy adults and acromegalics. Mean growth hormone (GH) levels were obtained for acromegalic patients. Differences were compared using t-tests (unadjusted) and multiple regression models (adjusted for age and gender). Correlations were expressed as Pearson's coefficient (r). RESULTS: For acromegalic patients, GH was significantly correlated with IGF-I ( $r = 0.50$ ;  $P < 0.001$ ) and IGFBP-3 ( $r = 0.29$ ;  $P = 0.03$ ) but not IGF-II or IGFBP-2. Contrary to expectations, mean IGF-II and IGFBP-2 levels were significantly raised in the acromegalics compared with normals [adjusted mean difference (95% CI) = 226 (181, 271) microg/l and 305 (200, 410) microg/l, respectively]. Ten acromegalic patients had colorectal neoplasia but their presence did not contribute to the elevations in serum IGF-II and IGFBP-2. The (IGF-I + IGF-II)/IGFBP-3 molar ratios were remarkably constant in both healthy adults and acromegalics, but the relationships of the ligands individually with IGFBP-3 were not linear: as IGFBP-3 increased, IGF-I also increased whereas IGF-II initially increased but then decreased. IGFBP-2 did not correlate with IGF-II, but molar concentration significantly correlated with the IGF-II/IGFBP-3 molar ratio ( $r = 0.40$ ;  $P = 0.001$ ). CONCLUSIONS: Serum IGF-II and IGFBP-2 levels were paradoxically elevated in acromegalics, independent of the presence of colorectal neoplasia. The (IGF-I + IGF-II)/IGFBP-3 molar ratio appears to be pivotal in determining IGF-II values, which, in turn, expressed as a ratio of IGFBP-3, is related to IGFBP-2. These observations offer new insights into the regulation of these peptides.

L3 ANSWER 4 OF 21 MEDLINE on STN  
ACCESSION NUMBER: 200126942 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 11063745  
TITLE: Synthesis and characterization of insulin-like growth factor (IGF)-1 photoprobes selective for the IGF-binding proteins (IGFBPs). photoaffinity labeling of the IGF-binding domain on IGFBP-2.  
AUTHOR: Horney M J; Evangelista C A; Rosenzweig S A  
CORPORATE SOURCE: Department of Cell and Molecular Pharmacology and Experimental Therapeutics, Medical University of South Carolina, Charleston 29425, USA.  
CONTRACT NUMBER: CA-78887 (United States NCI)  
SOURCE: The Journal of biological chemistry, (2001 Jan 26) Vol. 276, No. 4, pp. 2880-9. Electronic Publication: 2000-11-03.  
Journal code: 2985121R. ISSN: 0021-9258.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
(RESEARCH SUPPORT, NON-U.S. GOV'T)  
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200106  
ENTRY DATE: Entered STN: 25 Jun 2001  
Last Updated on STN: 5 Jan 2003

Entered Medline: 21 Jun 2001

AB Elevated insulin-like growth factor (IGF)-1 levels are prognostic for the development of prostate and breast cancers and exacerbate the complications of diabetes. In each case, perturbation of the balance between IGF-1/2, the IGF-1 receptor, and the IGF-binding proteins (IGFBPs) leads to elevated IGF-1 sensitivity. Blockade of IGF action in these diseases would be clinically significant. Unfortunately, effective IGF antagonists are currently unavailable. The IGFBPs exhibit high affinity and specificity for the IGFs and serve as natural IGF antagonists, limiting their mitogenic/anti-apoptotic effects. As an initial step in designing IGFBP-based agents that antagonize IGF action, we have begun to analyze the structure of the IGF-binding site on IGFBP-2. To this end, two IGF-1 photoprobes, N(alphaGly1)-(4-azidobenzoyl)-IGF-1 (abG(1)IGF-1) and N(alphaGly1)-((2-6-(biotinamido)-2(p-azidobenzamido)hexanoamido)ethyl-1,3'-dithiopropionoyl)-IGF-1 (bedG(1)IGF-1), selective for the IGFBPs were synthesized by derivatization of the alpha-amino group of Gly(1), known to be part of the IGFBP-binding domain. Mass spectrometric analysis of the reduced, alkylated, and trypsin-digested abG(1)IGF-1.recombinant human IGFBP-2 (rhIGFBP-2) complex indicated photoincorporation near the carboxyl terminus of rhIGFBP-2, between residues 266 and 287. Mass spectrometric analysis of avidin-purified tryptic peptides of the bedG(1)IGF-1.rhIGFBP-2 complex revealed photoincorporation within residues 212-227. Taken together, these data indicate that the IGFBP-binding domain on IGF-1 contacts the distal third of IGFBP-2, providing evidence that the IGF-1-binding domain is located within the C terminus of IGFBP-2.

L3 ANSWER 5 OF 21 MEDLINE on STN  
ACCESSION NUMBER: 2001198067 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 11238491  
TITLE: Diagnostic value of the acid-labile subunit in acromegaly: evaluation in comparison with insulin-like growth factor (IGF) I, and IGF-binding protein-1, -2, and -3.  
AUTHOR: Arosio M; Garrone S; Bruzzi P; Faglia G; Minuto F; Barreca A  
CORPORATE SOURCE: Institute of Endocrine Sciences, University of Milan, Ospedale Maggiore Istituto Ricovero e Cura a Carattere Scientifico, I-20122 Milan.  
SOURCE: The Journal of clinical endocrinology and metabolism, (2001 Mar) Vol. 86, No. 3, pp. 1091-8. Journal code: 0375362. ISSN: 0021-972X.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (COMPARATIVE STUDY)  
Journal; Article; (JOURNAL ARTICLE)  
(RESEARCH SUPPORT, NON-U.S. GOV'T)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 200104  
ENTRY DATE: Entered STN: 10 Apr 2001  
Last Updated on STN: 10 Apr 2001  
Entered Medline: 5 Apr 2001

AB In normal subjects the main form of circulating insulin-like growth factor (IGF) is the 150-kDa complex. This complex is formed by the IGF peptide, the acid-stable IGF-binding protein-3 (IGFBP-3), and the acid-labile subunit (ALS). Experimental and clinical data have demonstrated that ALS is primarily under the control of GH and plays a critical role in maintaining constant levels of circulating IGF-I. In this study we evaluated ALS, IGF-I, and IGFBP-1, -2, and -3 in 45 acromegalic patients in basal conditions and, in 37 of these, twice after surgical therapy compared with 100 age- and sex-matched control subjects to estimate their value as parameter of GH secretory state. The results demonstrated that

in acromegaly before treatment all parameters (ALS, 523 +/- 26; IGF-I, 129 +/- 6; IGFBP-1, 0.7 +/- 0.1; IGFBP-3, 234 +/- 21; nmol/L; mean +/- SEM) but IGFBP-2 were significantly different (P<0.0001) from those in healthy subjects (ALS, 281 +/- 4; IGF-I, 22 +/- 1; IGFBP-1, 1.6 +/- 0.1; IGFBP-3, 91 +/- 3). IGF-I was more sensitive (100%) than ALS (89%), and both were more predictive of disease status than IGFBP-3, in that 27% of the patients had IGFBP-3 levels within the normal range. Considering the ALS/IGFBP-3 molar ratio, almost 55% of ALS circulated in a free form in active acromegaly. Before treatment, the IGF-I/IGFBPs (-1 + -2 + -3) molar ratio, which can be regarded as free, biologically active, IGF-I, was greatly increased (0.77 +/- 0.06; P<0.0001) compared with that in control subjects (0.23 +/- 0.01). After surgery, all 10 patients with controlled disease showed normalization of ALS (100% sensitivity), whereas 9 of them had normal IGFBP-3; reevaluation after varying lengths of time showed all these parameters within the normal range. In the 27 patients with active disease, IGF-I and ALS were more predictive of disease status (91% and 83% negative predictive values, respectively) than IGFBP-3 (53%). The basal ALS concentration correlated only with IGFBP-3 (r = 0.70; P<0.001). In postsurgery samples (first control) a statistically significant (P<0.001) correlation was found between mean GH values as well as minimum GH after oral glucose tolerance test and ALS (r = 0.72 and 0.83, respectively), IGF-I (r = 0.69 and 0.77), IGFBP-3 (r = 0.50 and 0.72), and IGFBP-2 (r = -0.36 and -0.63). Similarly, IGF-I, IGFBP-3, and ALS were positively correlated among themselves and negatively correlated with IGFBP-2 (P<0.001). In conclusion, in the diagnosis of acromegaly, the measurement of total IGF-I appears to be the most sensitive parameter among the subunits of the 150K complex, and IGFBP-3 the least sensitive. For ALS, this subunit is quite sensitive and appears to be a useful parameter in reassessment after surgical treatment.

L3 ANSWER 6 OF 21 MEDLINE on STN  
 ACCESSION NUMBER: 1999371629 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 10444029  
 TITLE: Glomerular ultrafiltration of IGF-I may contribute to increased renal sodium retention in diabetic nephropathy.  
 AUTHOR: Wang S N; Lapage J; Hirschberg R  
 CORPORATE SOURCE: Division of Nephrology and Hypertension, Harbor-UCLA Medical Center, Torrance 90509, USA.  
 SOURCE: The Journal of laboratory and clinical medicine, (1999 Aug) Vol. 134, No. 2, pp. 154-60.  
 JOURNAL CODE: 0375375. ISSN: 0022-2143.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 (RESEARCH SUPPORT, NON-U.S. GOV'T)  
 LANGUAGE: English  
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
 ENTRY MONTH: 199908  
 ENTRY DATE: Entered STN: 27 Aug 1999  
 Last Updated on STN: 27 Aug 1999  
 Entered Medline: 19 Aug 1999

AB Insulin-like growth factor-I (IGF-I) is found in plasma at relatively high levels (approximately 40 nmol/L) but <1% is present in the free form and >99% is bound to specific binding proteins to form high-molecular-weight complexes of approximately 50 and approximately 150 kd. We hypothesized that in rats with diabetic nephropathy but not in normal animals, IGF-I-containing binding protein complexes undergo glomerular ultrafiltration, allowing the peptide to interact with IGF-I receptors in apical tubular membranes. By this route, ultrafiltered IGF-I may increase tubular epithelial cell sodium absorption in overt diabetic nephropathy. In serum samples from diabetic rats, IGF-I levels (227 +/- 34 ng/mL) were reduced as compared with control levels (319 +/- 33 ng/mL, P =

.05), and IGF-binding protein-2 (IGFBP-2) is increased about 2-fold. In diabetic rats, IGF-I undergoes glomerular ultrafiltration and is present in proximal tubular fluid that was collected by nephron micropuncture at  $2.54 \pm 0.54$  nmol/L but is below the detection limit in tubular fluid from normal rats. IGFBP-1, IGFBP-2, IGFBP-3, and IGFBP-4 are all present in diabetic rat glomerular ultrafiltrate, but IGFBP-2 levels are greater than those of each of the other three IGFBPs. Neither recombinant human IGF-I (1 nmol/L) nor diabetic rat glomerular ultrafiltrate affect sodium transport in cultured mouse proximal tubular cells. In contrast, rhIGF-I and diabetic rat glomerular ultrafiltrate increase the apical-to-basolateral transport of  $22\text{Na}^+$  in distal tubule-like A6 cells through mechanisms involving apical IGF-I receptors. In normal rats, luminal infusion with rhIGF-I or with diabetic rat glomerular ultrafiltrate into late proximal tubules increases distal tubular  $\text{Na}^+$  absorption. These findings indicate that diabetic glomerular sclerosis causes glomerular ultrafiltration of IGF-I, and they suggest that tubular fluid IGF-I may contribute to sodium (and fluid) retention that is commonly observed in patients with severe diabetic nephropathy.

L3 ANSWER 7 OF 21 MEDLINE on STN  
 ACCESSION NUMBER: 1999082968 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 9867079  
 TITLE: Growth hormone bioactivity, insulin-like growth factors (IGFs), and IGF binding proteins in obese children.  
 AUTHOR: Radetti G; Bozzola M; Pasquino B; Paganini C; Aglialoro A; Livieri C; Barreca A  
 CORPORATE SOURCE: Department of Paediatrics, Regional Hospital of Bolzano, Italy.  
 SOURCE: Metabolism: clinical and experimental, (1998 Dec) Vol. 47, No. 12, pp. 1490-3.  
 Journal code: 0375267. ISSN: 0026-0495.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199901  
 ENTRY DATE: Entered STN: 28 Jan 1999  
 Last Updated on STN: 28 Jan 1999  
 Entered Medline: 13 Jan 1999

AB In obese children, both spontaneous and stimulated growth hormone (GH) secretion are impaired but a normal or increased height velocity is usually observed. This study was undertaken to explain the discrepancy between impaired GH secretion and normal height velocity. We evaluated the GH bioactivity (GH-BIO), GH serum level by immunofluorimetric assay (GH-IFMA), insulin-like growth factor-I (IGF-I), IGF-II, and IGF binding protein-1 (IGFBP-1), IGFBP-2, and IGFBP-3 in 21 prepubertal obese children (13 boys and eight girls) aged 5.7 to 9.4 years affected by simple obesity and in 32 (22 boys and 10 girls) age- and sex-matched normal-weight controls. The results were as follows (obese versus [v] controls): GH-IFMA,  $4.84 \pm 3.54$  v  $23.7 \pm 2.04$  microg/L ( $P < .001$ ); GH-BIO,  $0.60 \pm 0.45$  v  $1.84 \pm 0.15$  U/mL ( $P < .001$ ); IGF-I,  $173.8 \pm 57.2$  v  $188.6 \pm 132.6$  ng/mL (nonsignificant); IGF-II,  $596.1 \pm 139.7$  v  $439.3 \pm 127.4$  ng/mL ( $P < .001$ ); IGFBP-1,  $23.25 \pm 14.25$  v  $107 \pm 165.7$  ng/mL ( $P < .05$ ); IGFBP-2,  $44.37 \pm 62.18$  v  $385.93 \pm 227.81$  ng/mL ( $P < .001$ ); IGFBP-3,  $3.31 \pm 0.82$  v  $2.6 \pm 0.94$  microg/mL ( $P < .05$ ); and IGFs/IGFBPs,  $1.32 \pm 0.32$  v  $1.07 \pm 0.34$  ( $P < .05$ ). In conclusion, in prepubertal obese children, not only immunoreactive but also bioactive GH concentrations were low. In these subjects, therefore, nutritional factors and insulin may contribute to sustain normal growth also by modulating several components of the IGF-IGFBP system.



L3 ANSWER 8 OF 21 MEDLINE on STN  
 ACCESSION NUMBER: 1999041581 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 9826208  
 TITLE: Gene expression of insulin-like growth factor-I, its receptor and binding proteins in retina under hypoxic conditions.  
 AUTHOR: Averbukh E; Weiss O; Halpert M; Yanko R; Moshe R; Nephesh I; Flyvbjerg A; Yanko L; Raz I  
 CORPORATE SOURCE: Department of Ophthalmology, Hadassah University Hospital, Jerusalem, Israel.  
 SOURCE: Metabolism: clinical and experimental, (1998 Nov) Vol. 47, No. 11, pp. 1331-6.  
 Journal code: 0375267. ISSN: 0026-0495.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 (RESEARCH SUPPORT, NON-U.S. GOV'T)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199812  
 ENTRY DATE: Entered STN: 15 Jan 1999  
 Last Updated on STN: 15 Jan 1999  
 Entered Medline: 2 Dec 1998

AB Hypoxia is the main stimulus for neovascularization in the retina. Insulin-like growth factor-I (IGF-I) is thought to be one of the mediators of this process. Severe persistent hypoxia, as occurs in central retinal artery occlusion, is associated with less retinal neovascularization than relative hypoxia. To study the influence of different types of hypoxia on the IGF system, we used a model of neonatal rat retina that responds with neovascularization to a relative hypoxic stimulus produced by alternating oxygen concentrations in the respired air. We studied the influence of 24-hour hypoxia (10% oxygen), 48-hour hyperoxia (75% oxygen), and relative hypoxia (shifting from 48 hours in 75% oxygen to 24 hours in room air) on the gene expression of IGF-I, IGF-I receptor (IGF-IR), and IGF binding protein-1 (IGFBP-1), IGFBP-2, and IGFBP-3 in retina using a solution hybridization RNase protection assay. Hypoxia induced a significant increase in retinal IGF-IR (178%), IGFBP-2 (227%), and IGFBP-3 (317%) mRNA; however, retinal IGF-I mRNA was reduced, as well as serum growth hormone (GH). Relative hypoxia caused a similar but less pronounced trend in the gene expression of IGF-IR and the binding proteins, whereas retinal IGF-I mRNA was unchanged and serum GH was elevated. Both hypoxia and relative hypoxia may cause IGF system stimulation in the retina through upregulation of IGF-IR and IGFBPs. This stimulation may result in neovascularization. However, during hypoxia, low levels of tissue oxygenation and reduced local production of IGF-I may impede the neovascularization process.

L3 ANSWER 9 OF 21 MEDLINE on STN  
 ACCESSION NUMBER: 1998319446 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 9657364  
 TITLE: Endurance training and its effect upon the activity of the GH-IGFs system in the elderly.  
 AUTHOR: Deuschle M; Blum W F; Frystyk J; Orskov H; Schweiger U; Weber B; Korner A; Gotthardt U; Schmider J; Standhardt H; Heuser I  
 CORPORATE SOURCE: Max Planck Institute of Psychiatry, Clinical Institute, Munchen, Germany.  
 SOURCE: International journal of sports medicine, (1998 May) Vol. 19, No. 4, pp. 250-4.  
 Journal code: 8008349. ISSN: 0172-4622.  
 PUB. COUNTRY: GERMANY; Germany, Federal Republic of  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199809  
ENTRY DATE: Entered STN: 6 Oct 1998  
Last Updated on STN: 6 Oct 1998  
Entered Medline: 22 Sep 1998

AB There is an age-associated decline in the activity of the GH-IGFs system. However, so far, it has not been studied, whether this decline in somatotrophic activity might be preventable by intensive exercising. We studied 11 elderly male (50-78 years) marathon runners and 10 age-matched male (52-73 years) sedentary controls to evaluate plasma concentrations of GH, total and free IGF-I and IGF-II and of IGF-binding protein-1 (IGFBP-1), IGFBP-2, IGFBP-3 and insulin. When comparing the two groups (runners vs controls) no differences were found in GH ( $1.0 \pm 1.2$  vs  $1.3 \pm 1.3$  microg/l [mean  $\pm$  SD]), IGF-1 ( $115 \pm 23$  vs  $113 \pm 21$  microg/l), IGF-II ( $961 \pm 192$  vs  $864 \pm 125$  microg/l), free IGF-1 ( $227 \pm 80$  vs  $318 \pm 146$  ng/l), free IGF-II ( $563 \pm 249$  vs  $492 \pm 108$  ng/l), IGFBP-3 ( $2403 \pm 515$  vs  $2307 \pm 326$  microg/l) or insulin ( $26 \pm 13$  vs  $27 \pm 18$  mU/l). However, IGFBP-1 ( $4.44 \pm 2.61$  vs  $2.28 \pm 0.93$  microg/l) and IGFBP-2 ( $493 \pm 143$  vs  $340 \pm 186$  microg/l) were found to be significantly increased in marathon runners. In conclusion, our findings do not support the hypothesis that the age-associated decline in GH, IGF-1 and IGFBP-3 may be preventable by intensive endurance training. However, marathon running affects the regulation of the GH-IGFs system activity at the level of IGFBP-1 and -BP-2.

L3 ANSWER 10 OF 21 MEDLINE on STN  
ACCESSION NUMBER: 97033831 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 8879489  
TITLE: Depletion of insulin in streptozocin-induced-diabetic pigs alters estradiol, insulin-like growth factor (IGF)-I and IGF binding proteins in cultured ovarian follicles.  
AUTHOR: Edwards J L; Hughey T C; Moore A B; Cox N M  
CORPORATE SOURCE: Department of Animal and Dairy Sciences, Mississippi State University, Mississippi 39762, USA.  
SOURCE: Biology of reproduction, (1996 Oct) Vol. 55, No. 4, pp. 775-81.  
Journal code: 0207224. ISSN: 0006-3363.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (COMPARATIVE STUDY)  
(Journal; Article; (JOURNAL ARTICLE)  
(RESEARCH SUPPORT, NON-U.S. GOV'T)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199701  
ENTRY DATE: Entered STN: 19 Feb 1997  
Last Updated on STN: 29 Jan 1999  
Entered Medline: 30 Jan 1997

AB The objectives were to investigate whether insulin-dependent diabetes mellitus disrupts production of estradiol and activity of the insulin-like growth factor (IGF)-I system in individual ovarian follicles during the preovulatory period of the estrous cycle. Diabetes mellitus was induced with streptozocin (150 mg/kg) in seven cyclic gilts at 180  $\pm$  5 days of age. On Day 12 of the estrous cycle, insulin replacement therapy was withdrawn from three gilts and continued in four; four gilts served as normal controls. After ovary removal on Day 18, all follicles  $>$  or  $=$  3 mm diameter were dissected free and cultured for 6 h in the presence of 280 ng testosterone for assessment of estradiol and IGF-I production and binding protein activity. Treatments did not affect corpora lutea number ( $15.4 \pm 0.8$ ) or serum estradiol ( $5.8 \pm 0.8$  pg/ml) on Day 18. There were no differences for any measure of follicular development between

normal and insulin-treated diabetic gilts. Untreated diabetic gilts, compared to normal and insulin-treated diabetic gilts, had fewer total visible follicles (22.7 vs. 61.3 and 63.3; SEM = 8;  $p < 0.01$ ) and reduced follicular diameter (3.4 vs. 4.4 and 4.2 mm; SEM = 0.3;  $p < 0.0001$ ), respectively. Untreated diabetic gilts had a greater percentage of macroscopically atretic follicles than normal and insulin-treated diabetic gilts (75% vs. 47% and 36%; SEM = 10;  $p < 0.05$ ). Untreated diabetes mellitus lowered estradiol ( $p < 0.01$ ); however, effects of treatment on estradiol production were not significant when diameter was part of statistical models. When contents of IGF-I in follicular fluid and conditioned medium were summed after 6 h of culture, untreated diabetic pigs had lower IGF-I at all follicle diameters than pigs in the other treatments ( $p < 0.05$ ). IGF binding protein (BP) activity was affected by diabetes mellitus, with untreated diabetic pigs having greater IGFBP-1 activity in medium and with both diabetic groups having greater IGFBP-2 activity in follicular fluid ( $p < 0.05$ ). Activity of IGFBP-1 predominated in conditioned medium, and IGFBP-2 activity predominated in follicular fluid. IGFBP-3 was decreased in follicular fluid of atretic follicles and in medium of atretic follicles in all except the insulin-treated diabetic gilts; in these gilts it was increased in atretic follicles (treatment by atresia interaction;  $p < 0.05$ ). In conclusion, estradiol was most related to size of the follicle; however, lowering of IGF-I regardless of follicle diameter and alterations in IGFBP activity suggest that diabetes affects IGF-I and its binding proteins differently from estradiol production. These alterations may explain reduced follicular growth and increased follicular atresia in diabetic pigs.

L3 ANSWER 11 OF 21 MEDLINE on STN  
 ACCESSION NUMBER: 96210868 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 8626847  
 TITLE: Insulin-like growth factor-I (IGF-I) and IGF-binding proteins in children with nephrotic syndrome.  
 AUTHOR: Lee D Y; Park S K; Kim J S  
 CORPORATE SOURCE: Department of Pediatrics, Chonbuk National University Medical School, Chonju, Korea.  
 SOURCE: The Journal of clinical endocrinology and metabolism, (1996 May) Vol. 81, No. 5, pp. 1856-60. Journal code: 0375362. ISSN: 0021-972X.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)  
 LANGUAGE: English  
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
 ENTRY MONTH: 199606  
 ENTRY DATE: Entered STN: 8 Jul 1996  
 Last Updated on STN: 8 Jul 1996  
 Entered Medline: 21 Jun 1996

AB Growth failure appears to be a major problem for nephrotic children who fail to respond to steroid therapy. Recently altered serum insulin-like growth factor (IGF) and IGF-binding protein (IGFBP) profiles are reported in renal failure and glomerulonephritis. In this study, the serum IGFBP profile was evaluated by Western ligand blot and RIA in 22 patients with the nephrotic syndrome. Serum IGFBP-3 was decreased, whereas IGFBP-2 was increased in most patients with the nephrotic syndrome. The mean serum IGFBP-3 level was  $2123 \pm 531$  ng/mL in active states and was increased to a normal level ( $3593 \pm 407$  ng/mL) in remission states. We also measured serum IGF-I by RIA. The serum concentration of IGF-I (mean  $\pm$  SD) was  $67.4 \pm 23.2$  ng/mL in active states and was increased to  $127.1 \pm 21.8$  ng/mL in remission states, but was still lower than that in control subjects ( $180.4 \pm 15.8$  ng/mL). IGF-I and IGFBP-3 levels were not correlated with primary renal

diseases or the amount of proteinuria. For serum IGF-IGFBP complexes, 150-kDa complexes were significantly decreased in patients with the nephrotic syndrome compared with those in control subjects. In urine from nephrotic syndrome patients, 150- and 50-kDa complexes were found, whereas these complexes did not exist in the urine of control subjects. We speculate that low serum IGF-I and IGFBP-3 levels would be partially due to the increased urinary losses of serum IGF-IGFBP complexes, especially that of 150 kDa, and these changes may contribute to growth failure in persistent nephrotic syndrome.

L3 ANSWER 12 OF 21 MEDLINE on STN  
 ACCESSION NUMBER: 96043399 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 7485487  
 TITLE: Insulin regulates circulating insulin-like growth factors and some of their binding proteins in lactating cows.  
 AUTHOR: McGuire M A; Dwyer D A; Harrell R J; Bauman D E  
 CORPORATE SOURCE: Department of Animal Sciences, Cornell University, Ithaca, New York 14853, USA.  
 SOURCE: The American journal of physiology, (1995 Oct) Vol. 269, No. 4 Pt 1, pp. E723-30.  
 Journal code: 0370511. ISSN: 0002-9513.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 (RESEARCH SUPPORT, NON-U.S. GOV'T)  
 (RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199512  
 ENTRY DATE: Entered STN: 24 Jan 1996  
 Last Updated on STN: 24 Jan 1996  
 Entered Medline: 12 Dec 1995

AB Four lactating Holstein cows were subjected to a hyperinsulinemic-euglycemic clamp to evaluate the effects of insulin on circulating concentrations of insulin-like growth factors (IGF) and their binding proteins (IGFBP). Baseline blood samples were taken every 4 h for 2 days. For the 4-day clamp, insulin was infused (1 microgram.kg body wt-1.h-1) into the jugular vein and exogenous glucose was infused to maintain euglycemia. Circulating insulin was increased approximately fivefold, while glucose was maintained within 10% of baseline concentrations by infusion of 0.15 g.kg body wt-1.h-1 glucose. Hyperinsulinemia-euglycemia approximately doubled IGF-I (145 vs. 286 ng/ml, SE = 20) while decreasing circulating IGF-II (285 vs. 180 ng/ml, SE = 32). Densitometry of Western blots demonstrated no change in IGFBP-3 or a 30,000 relative molecular weight (M(r)) band during the clamp. However, IGFBP-2 decreased 73% and a 26,000 M(r) band decreased 58% by the end of the clamp. Therefore, insulin, directly or via secondary changes, increased circulating concentrations of IGF-I while decreasing concentrations of IGF-II, IGFBP-2, and a 26,000 M(r) IGFBP in lactating cows.

L3 ANSWER 13 OF 21 MEDLINE on STN  
 ACCESSION NUMBER: 95155522 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 7531712  
 TITLE: Effects of caloric or protein restriction on insulin-like growth factor-I (IGF-I) and IGF-binding proteins in children and adults.  
 AUTHOR: Smith W J; Underwood L E; Clemmons D R  
 CORPORATE SOURCE: Department of Medicine, University of North Carolina School of Medicine, Chapel Hill 27599.  
 CONTRACT NUMBER: HD-26871 (United States NICHD)  
 HD-28081 (United States NICHD)

SOURCE: The Journal of clinical endocrinology and metabolism,  
(1995 Feb) Vol. 80, No. 2, pp. 443-9.  
Journal code: 0375362. ISSN: 0021-972X.

PUB. COUNTRY: United States

DOCUMENT TYPE: (COMPARATIVE STUDY)  
Journal; Article; (JOURNAL ARTICLE)  
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 199503

ENTRY DATE: Entered STN: 22 Mar 1995

Last Updated on STN: 29 Jan 1996

Entered Medline: 10 Mar 1995

AB Serum concentrations of insulin-like growth factor-I (IGF-I) and IGF-binding protein-1 (IGFBP-1), -2, and -3 are influenced by dietary intake in normal adults. These studies were undertaken to determine the influence of dietary factors on these proteins in children and to compare the responses in children to those in adults. Eight adults and eight pubertal children underwent energy restriction (50% reduction intake) for 6 days and were refed a normal diet for an additional 6 days. Basal energy intakes during the prerestriction periods were 70 Cal/kg in children and 35 Cal/kg in adults. A second group of 8 adults and 6 children underwent protein restriction (decreased from 1.0 to 0.66 g/kg in both groups) for 6 days and were refed a normal diet for 6 days. Calorie restriction resulted in a significant decrease in nitrogen balance in adults and children. Likewise, IGF-I concentrations declined significantly in both adults and children. In contrast, IGFBP-1 concentrations were significantly increased in adults (from 40 +/- 6 to 62 +/- 4 ng/mL;  $P < 0.05$ ), but not in children. Serum concentrations of IGFBP-2 did not change in either group in response to energy restriction. IGFBP-3 declined significantly in the children (3189 +/- 90 to 2843 +/- 96 ng/mL;  $P < 0.05$ ), but not in the adults. Protein restriction also caused negative nitrogen balance in both children and adults and a decline in the mean IGF-I concentration in the adults. IGFBP-2 concentrations rose significantly in both adults (131 +/- 15 to 164 +/- 15 ng/mL;  $P < 0.005$ ) and children (126 +/- 13 to 158 +/- 15 ng/mL;  $P < 0.05$ ) in response to protein restriction and returned to normal during refeeding. IGFBP-3 was slightly, but significantly, reduced in response to protein restriction in adults (3518 +/- 180 to 3328 +/- 151 ng/mL;  $P < 0.05$ ), but not children. The findings indicate that protein or energy restriction in children leads to changes in IGF-I or specific IGFBPs. Changes in IGFBP-2 are sensitive to protein restriction, and measurement of IGFBP-2 may be useful in monitoring the response to refeeding in children who have been ingesting suboptimal amounts of protein.

L3 ANSWER 14 OF 21 MEDLINE on STN

ACCESSION NUMBER: 95099040 MEDLINE

DOCUMENT NUMBER: PubMed ID: 7528435

TITLE: Role of GH and IGF-I in the regulation of IGF-I, IGF-I receptor and IGF binding protein gene expression in the rat spleen.

AUTHOR: Domene H M; Meidan R; Yakar S; Shen-Orr Z; Cassorla F; Roberts C T Jr; LeRoith D

CORPORATE SOURCE: Diabetes Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892.

SOURCE: Regulatory peptides, (1994 Aug 4) Vol. 52, No. 3, pp. 215-26.

Journal code: 8100479. ISSN: 0167-0115.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199501  
ENTRY DATE: Entered STN: 15 Feb 1995  
Last Updated on STN: 3 Mar 2000  
Entered Medline: 20 Jan 1995

AB To characterize the expression of the IGF-I system in the spleen and its role in spleen growth, we have studied the effect of hypophysectomy and the action of either GH or IGF-I treatment on the expression of several components of the IGF system in the rat. Female Sprague-Dawley rats were hypophysectomized (Hx) on postnatal day 50, and five animals each received twice-daily sc injections of saline, bovine GH (bGH; 84 micrograms/animal/day), or recombinant human IGF-I (rhIGF-I; 125 micrograms/animal/day) for 11 days. Compared to sham-operated controls, Hx animals exhibited a reduction in both body (192.6 +/- 5.6 g (mean +/- S.E.M.) vs. 268.6 +/- 6.0 g;  $P < 0.001$ ) and spleen weights (0.42 +/- 0.03 g vs. 0.84 +/- 0.06 g;  $P < 0.001$ ). The reduction in body and spleen weights in Hx animals was partially prevented by both bGH and rhIGF-I. Body weights were 234.2 +/- 5.3 g ( $P < 0.001$ ) after bGH and 213.8 +/- 6.3 g ( $P < 0.05$ ) after rhIGF-I. Spleen weights were 0.56 +/- 0.048 after bGH  $P < 0.01$  and 0.53 +/- 0.05 g after rhIGF-I ( $P < 0.05$ ). Serum GH and IGF-I levels were markedly reduced in Hx animals and bGH partially maintained IGF-I levels. Hypophysectomy reduced spleen IGF-I mRNA levels (30.6 +/- 7.5% of control values;  $P < 0.05$ ) and this reduction was prevented by bGH (96.6 +/- 24.2%; NS) but not by rhIGF-I (39.9 +/- 5.0% NS vs. Hx). There were no changes in GH receptor or IGF-I receptor mRNA levels in Hx or bGH or rhIGF-I-treated animals. When IGF-I binding protein (IGFBP) mRNA levels were studied under these conditions, we found that IGFBP-1 mRNA was not detected in spleen; IGFBP-2 mRNA levels were reduced in Hx rats (67.9 +/- 7.4% of control values,  $P < 0.05$ ) and bGH treatment prevented this reduction (95.5 +/- 12.2%, NS). IGFBP-3 mRNA levels were not affected by hypophysectomy or by bGH treatment, but were reduced in rhIGF-treated rats (69.6 +/- 3.0%,  $P < 0.05$ ). On the other hand, IGFBP-4 mRNA levels were increased in Hx rats (136.4 +/- 15.9% of control values,  $P < 0.05$ ) and bGH treatment prevented this increase. (ABSTRACT TRUNCATED AT 250 WORDS)

L3 ANSWER 15 OF 21 MEDLINE on STN  
ACCESSION NUMBER: 95045221 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 7525259  
TITLE: Insulin-like growth factor-binding protein-2 and -3 are correlated with atresia and preovulatory maturation in the porcine ovary.  
AUTHOR: Grimes R W; Guthrie H D; Hammond J M  
CORPORATE SOURCE: Department of Medicine, Milton S. Hershey Medical Center, Pennsylvania State University, Hershey 17033.  
CONTRACT NUMBER: R01-HD24565 (United States NICHD)  
SOURCE: Endocrinology, (1994 Nov) Vol. 135, No. 5, pp. 1996-2000.  
Journal code: 0375040. ISSN: 0013-7227.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (COMPARATIVE STUDY)  
Journal; Article; (JOURNAL ARTICLE)  
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)  
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)

LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 199412  
ENTRY DATE: Entered STN: 10 Jan 1995  
Last Updated on STN: 29 Jan 1996  
Entered Medline: 16 Dec 1994

AB We compared insulin-like growth factor-binding protein (IGFBP) levels with

indicators of follicular maturation and atresia in individual follicles of the porcine ovary. Follicular development was synchronized with the progestin, altrenogest, and progestin withdrawal was used to initiate the growth of an ovulatory cohort of follicles, which is accompanied by atresia of noncohort follicles. Individual follicles were isolated on days 1, 3, 5, and 7 after progestin withdrawal. Atretic follicles were identified by the presence of low hypodiploid levels of DNA in 10% or more of their granulosa cells using flow cytometry. The follicular fluid (FF) level of IGFBP-3 did not differ significantly between healthy and atretic medium-sized (3- to 6-mm) follicles and was not significantly correlated with the percentage of granulosa cells containing hypodiploid levels of DNA ( $r = 0.181$ ) or with endocrine parameters such as FF concentrations of estradiol or androstenedione. However, among healthy follicles (atretic follicles removed from analyses to better examine follicular maturation), IGFBP-3 increased ( $P < 0.01$ ) between days 1 and 7 and was positively correlated with follicle diameter ( $r = 0.514$ ;  $P < 0.05$ ) and the FF concentration of progesterone ( $r = 0.556$ ;  $P < 0.01$ ), indicators of the degree of follicular maturation. FF IGFBP-2 levels were 3-fold greater ( $P < 0.01$ ) in atretic than in healthy follicles, and IGFBP-2 was correlated with percentage of granulosa cells containing hypodiploid levels of DNA ( $r = 0.729$ ;  $P < 0.001$ ). Among healthy follicles, FF IGFBP-2 did not differ significantly among days and was not significantly correlated with follicle diameter. These data suggest that the content of IGFBP-2 is related to the state of follicular health/atresia, whereas IGFBP-3 is related to preovulatory follicular development.

L3 ANSWER 16 OF 21 MEDLINE on STN  
 ACCESSION NUMBER: 94043353 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 7693708  
 TITLE: Three clustered Sp1 sites are required for efficient transcription of the TATA-less promoter of the gene for insulin-like growth factor-binding protein-2 from the rat.  
 AUTHOR: Boisclair Y R; Brown A L; Casola S; Rechler M M  
 CORPORATE SOURCE: Growth and Development Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892.  
 SOURCE: The Journal of biological chemistry, (1993 Nov 25) Vol. 268, No. 33, pp. 24892-901.  
 Journal code: 2985121R. ISSN: 0021-9258.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 (RESEARCH SUPPORT, NON-U.S. GOV'T)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 OTHER SOURCE: GENBANK-M58560  
 ENTRY MONTH: 199312  
 ENTRY DATE: Entered STN: 17 Jan 1994  
 Last Updated on STN: 29 Jan 1996  
 Entered Medline: 20 Dec 1993

AB Insulin-like growth factor-binding protein-2 (IGF-BP-2) transcription in rat liver varies with developmental age and fasting. To define the DNA elements required for efficient expression of the TATA-less rat IGFBP-2 gene, the native or mutated promoter was fused to a promoterless luciferase reporter gene and transfected into BRL-3A rat liver and 293 human embryonic kidney cell lines. Luciferase activity decreased approximately 25-fold with progressive 5' promoter deletions from nucleotide (nt) -581 to nt -189 (relative to ATG, +1). The smallest construct, however, still had > 21-fold greater luciferase activity than the promoterless construct. In DNase I foot-printing assays using native nt -276 to -36 promoter fragments or fragments containing block substitution mutations, BRL-3A nuclear extract and purified human

transcription factor Sp1 protected a region from nt -234 to -215 containing one GC box and a broad region from nt -189 to -125 that contained three clustered but independent GC boxes. In gel retardation assays using an Sp1 oligonucleotide probe, BRL-3A extract formed two closely migrating complexes that were immunologically related to Sp1; Sp1 gave a single complex that co-migrated with the more retarded BRL-3A complex. Binding was competitively inhibited by oligonucleotides corresponding to each of the four GC boxes. The proximal three GC boxes were sufficient to allow trans-activation of the IGFBP-2 promoter by Sp1 in *Drosophila* SL2 cells. Independent block mutations indicated that all three of the GC boxes are required for promoter activity and are equally important. Thus, binding of Sp1 or Sp1-related proteins to three clustered GC boxes in the proximal IGFBP-2 promoter is essential for promoter activity. Multiple upstream regions also contribute to the full expression of the IGFBP-2 gene.

L3 ANSWER 17 OF 21 MEDLINE on STN  
 ACCESSION NUMBER: 93185936 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 7680327  
 TITLE: Cloning and characterization of the gene encoding murine insulin-like growth factor-binding protein-2, mIGFBP-2.  
 AUTHOR: Landwehr J; Kaupmann K; Heinrich G; Schwander J  
 CORPORATE SOURCE: Zentrum fur Lehre und Forschung, Kantonsspital, Basel, Switzerland.  
 SOURCE: Gene, (1993 Feb 28) Vol. 124, No. 2, pp. 281-6.  
 Journal code: 7706761. ISSN: 0378-1119.  
 PUB. COUNTRY: Netherlands  
 DOCUMENT TYPE: (COMPARATIVE STUDY)  
 (Journal; Article; (JOURNAL ARTICLE)  
 (RESEARCH SUPPORT, NON-U.S. GOV'T)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 OTHER SOURCE: GENBANK-L03650; GENBANK-L03651; GENBANK-L03652;  
 GENBANK-L03653; GENBANK-L03654; GENBANK-L05436;  
 GENBANK-L05437; GENBANK-L05438; GENBANK-L05439;  
 GENBANK-S56520  
 ENTRY MONTH: 199304  
 ENTRY DATE: Entered STN: 16 Apr 1993  
 Last Updated on STN: 29 Jan 1996  
 Entered Medline: 5 Apr 1993  
 AB We present a characterization of the single-copy gene, mIGFBP-2, encoding the murine insulin-like growth factor-binding protein-2 (mIGFBP-2). It consists of four exons with sizes of 470 +/- 2, 227, 141 and > 475 nucleotides (nt). The first intron spans 23 kb of genomic sequence, and the complete gene extends to more than 28 kb. Two kb of the 5'-flanking region were sequenced. This region has no TATA or CAAT boxes but is G+G-rich and contains several potential regulatory sequence motifs. A total of five GC boxes, which may serve as potential binding sites for a transcription factor, Sp1, are present immediately upstream of the transcription start point (tsp). By primer extension, we identified a single tsp at nt position -85 +/- 2. The murine IGFBP-2 locus was mapped to the proximal region of mouse chromosome 1, to a region of conserved synteny with human chromosome 2q. A comparison of the deduced amino acid sequences of mouse, rat and human IGFBP-2 reveals a high degree of homology between all three species.

L3 ANSWER 18 OF 21 MEDLINE on STN  
 ACCESSION NUMBER: 92176866 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 1541918  
 TITLE: Serum half-life and in-vivo actions of recombinant bovine placental lactogen in the dairy cow.



AUTHOR: Byatt J C; Eppard P J; Veenhuizen J J; Sorbet R H; Buonomo F C; Curran D F; Collier R J  
 CORPORATE SOURCE: Monsanto Company, St Louis, Missouri 63198.  
 SOURCE: The Journal of endocrinology, (1992 Feb) Vol. 132, No. 2, pp. 185-93.  
 Journal code: 0375363. ISSN: 0022-0795.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 DOCUMENT TYPE: (COMPARATIVE STUDY)  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199204  
 ENTRY DATE: Entered STN: 24 Apr 1992  
 Last Updated on STN: 24 Apr 1992  
 Entered Medline: 7 Apr 1992

AB The clearance rate of recombinant bovine placental lactogen (rbPL) from the blood serum of four lactating dairy cows was measured using a specific radioimmunoassay. Two animals were non-pregnant, while the other two were at approximately 120 days of gestation. The rbPL was administered as an i.v. bolus injection (4 mg total) via an indwelling jugular catheter. Blood samples were taken periodically for 180 min and assayed for rbPL. Analysis of the clearance curves for the bolus injection suggested a single-compartment model and a serum half-life of 7.25 min. In a second experiment with the same animals, following cessation of lactation, rbPL or bovine GH (bGH) were administered by s.c. injection (50 mg/day) for 5 consecutive days. Blood samples were taken twice per day during the treatment period and a 3-day pretreatment period. Samples were analysed for glucose, blood urea nitrogen (BUN), non-esterified fatty acids (NEFA), creatinine, insulin, insulin-like growth factor-I (IGF-I) and IGF-II, tri-iodothyronine (T3), progesterone and IGF-binding protein-2 (IGFBP-2) to determine whether rbPL mediates similar metabolic effects to those of bGH. Administration of bGH stimulated an increase in NEFA, glucose, T3 and insulin, whereas none of these variables was affected by rbPL. The plasma concentrations of IGF-I and IGF-II were both increased by treatment with rbPL but, to a lesser extent than occurred with bGH. Interestingly, BUN and IGFBP-2 concentrations were reduced equally by bGH and rbPL. These results suggest that rbPL does not necessarily act as a GH agonist but, rather, may have distinct effects on intermediary metabolism that could be mediated through another specific receptor.

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ACCESSION NUMBER: 1997253495 EMBASE  
 TITLE: Characterization of truncated insulin-like growth factor-binding protein-2 in human milk.  
 AUTHOR: Jean Ho P.; Baxter R.C.  
 CORPORATE SOURCE: Dr. P.J. Ho, Kolling Inst. of Medical Research, Royal North Shore Hospital, St. Leonards, NSW 2065, Australia.  
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AB Truncated forms of insulin-like growth factor (IGF)-binding protein-2 (

IGFBP-2) have been purified from human milk and shown to retain partial IGF- binding activity. By affinity chromatography on agarose-IGF-I and HPLC, truncated IGFBP-2 of apparent M(r) 14,000,16,000 resolved into two peaks. Both peaks bound radioiodinated IGF-II on ligand blotting. Within both peaks, two sequences were identified, starting at Gly(169) and Lys(181) of hIGFBP-2 (predicted M(r), 13,786 and 12,502, respectively, if both extend to Gln(289)). Mass spectrometry of a fraction predominantly containing Gly(169) peptides yielded two major species, 13,840 and 13,425 M(r). Prolonged incubation of radioiodinated recombinant human (rh) IGFBP-2 with human milk failed to reveal any degradation, suggesting the formation of the fragments within the mammary gland. By solution binding assay, truncated IGFBP-2 showed less than 10% binding of [(125)I]IGF-I and 25% binding of [(125)I]IGF-II at pH 7.0 compared with rhIGBPB-2. No binding activity was seen at pH 4.0, in contrast to intact IGFBP-2, which showed peak binding from pH 4.0 to at least pH 9.0. The IGF-II association constant for truncated IGFBP-2 (6.5 nM(-1)) was 10-fold lower than that for intact IGFBP-2 (58 nM(-1)). Des(1-6)-IGF-II was totally inactive in displacing IGF-II tracer from the IGFBP-2 fragment, but displaced tracer from rhIGFBP-2 with 10% the activity of IGF-II. Thus, the amino-terminal hexapeptide of IGF-II is required for interaction with the carboxy-terminal domain of IGFBP-2. The presence of active IGFBP-2 fragments in milk suggests a role for milk IGFBP- 2 in modifying IGF activity in the neonatal gut.

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ACCESSION NUMBER: 1995331650 EMBASE

TITLE: Insulin regulates circulating insulin-like growth factors and some of their binding proteins in lactating cows.

AUTHOR: McGuire M.A.; Dwyer D.A.; Harrell R.J.; Bauman D.E.

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SOURCE: American Journal of Physiology - Endocrinology and Metabolism, (1995) Vol. 269, No. 4 32-4, pp. E723-E730.

ISSN: 0193-1849 CODEN: AJFMD9

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 002 Physiology

003 Endocrinology

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AB Four lactating Holstein cows were subjected to a hyperinsulinemic-euglycemic clamp to evaluate the effects of insulin on circulating concentrations of insulin-like growth factors (IGF) and their binding proteins (IGFBP). Baseline blood samples were taken every 4 h for 2 days. For the 4-day clamp, insulin was infused (1 µg .ovrhdot. kg body wt(-1) .ovrhdot. h(-1)) into the jugular vein and exogenous glucose was infused to maintain euglycemia. Circulating insulin was increased approximately fivefold, while glucose was maintained within 10% of baseline concentrations by infusion of 0.15 g .ovrhdot. kg body wt(-1) .ovrhdot. h(-1) glucose. Hyperinsulinemia-euglycemia approximately doubled IGF-I (145 vs. 286 ng/ml, SE = 20) while decreasing circulating IGF- II (285 vs. 180 ng/ml, SE = 32). Densitometry of Western blots demonstrated no change in IGFBP-3 or a 30,000 relative molecular weight (M(r)) band during the clamp. However, IGFBP-2 decreased 73% and a 26,000 M(r) band decreased 58% by the end of the clamp. Therefore,

insulin, directly or via secondary changes, increased circulating concentrations of IGF-I while decreasing concentrations of IGF-II, IGFBP-2, and a 26,000 M(r) IGFBP in lactating cows.

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ACCESSION NUMBER: 1992229511 EMBASE

TITLE: Nutrition and somatomedin XXIX: Molecular regulation of IGFBP-1 in hepatocyte primary culture.

AUTHOR: Villafuerte B.C.; Goldstein S.; Robertson D.G.; Pao C.-I.; Murphy L.J.; Phillips L.S.

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SOURCE: Diabetes, (1992) Vol. 41, No. 7, pp. 835-842.

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AB The insulinlike growth factors (IGFs) circulate in association with insulinlike growth factor binding proteins (IGFBPs) that modulate IGF action, but mechanisms of IGFBP regulation are poorly understood. We investigated the regulation of IGFBPs in primary cultures of rat hepatocytes, measuring the appearance of export proteins by ligand blotting after separation via SDS/PAGE, and evaluating mRNA with cDNA probes. Northern blotting studies revealed that IGFBP-1 was expressed at high levels in cultured hepatocytes, in which sustained release of both insulinlike growth factor I and albumin marks preservation of differentiated status. In contrast, transcripts of IGFBP-3 and IGFBP-2 were not detected. Release of IGFBP-1 was unaffected by exposure to glucose (20-500 mg/dl) or to provision of amino acids (0.25-6.25 times normal rat arterial plasma levels). Hormonal studies revealed little effect of glucagon, inhibition by insulin, stimulation by dexamethasone, and blunting of dexamethasone effects by added insulin. Adding dexamethasone provided progressive stimulation: 5-, 11-, and 26-fold at 10(-9), 10(-8), and 10(-7) M, all  $P < 0.01$ ; increases in IGFBP-1 protein (ligand blot) and IGFBP-1 mRNA (Northern blot) were highly correlated ( $r = 0.62$ ,  $P < 0.001$ ). In contrast, adding insulin resulted in progressive suppression of both IGFBP-1 protein and IGFBP-1 mRNA, 43% at 10(-10) M, 74% at 10(-9) M, and 83% (maximal) at 10(-8) M; ED(50) of 10(-10) M is within the physiological range of insulin concentrations. Directly adding growth hormone and insulinlike growth factor I had little effect, whereas adding insulinlike growth factor I attenuated the effect of insulin to decrease IGFBP-1 release. Exposure to insulin at 10(-6) M did not change IGFBP-1 gene expression at 30 min, but suppressed IGFBP-1 mRNA 37% at 90 min and 97% at 180 min ( $t(1/2) \sim 110$  min). IGFBP-1 release by normal rat hepatocytes is stimulated by dexamethasone and inhibited by insulin, apparently modulated at pretranslational levels. This system should be useful for further studies of biological regulation and underlying molecular mechanisms.

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